USAMMDA

Developing Quality Medical Products for U.S. Forces

Annual Report for CY 2004

- Administrative Services
- Regulatory Affairs
- Applied Medical Systems
- Pharmaceutical Systems
- Clinical Trial Monitoring
- Medical Affairs
- Force Health Protection

PROTECT
PROJECT - SUSTAIN

Table of Contents

Table of Contents 3
Commander's Message 5
Our Mission 6
Our Vision 6
Our Personnel 6
2002 PERSONNEL PROFILE 7
Administrative Services Office 8
Fiscal 2004 Performance 8
Fiscal 2004 Program Execution 10
Computer Support 11
Medical Affairs Division 12
Force Health Protection Branch 12
Introduction 12
Military Relevance 12
Accomplishments 13
Emergency Use Authorization 13
Force Health Protection Related Accomplishments 14
Educational Training and Regulatory Affairs Activities 15
Regulatory Affairs Division 16
Introduction 16
Military Relevance 16
Accomplishments (Includes RA activities as part of RCQ) 16
Quality Assurance/Clinical Trial Monitoring Branch 19
Introduction 19
Staffing 19
Tasks 19
Monitoring Special Immunization Program (SIP) Protocols at USAMRIID 19
Establish and Monitor Regulatory Files for Force Health Protection Contingency Protocols 20
Monitoring of Protocols not SIP or Contingency 20
External Collaboration 21
Special Tasks 21
Influenza (Flu) Vaccine Clinical Trial 21
Service on HSRRB: 22
Applied Medical Systems Project Management Division 22
Introduction 22
Military Relevance 23
Cartledge Infuser 23
Ceramic Oxygen Generator 24

Critical Care System for Trauma and Transport 24
Dental Field Treatment and Operating System 25
Field Sterilizer Improvement Device 25
Future Combat Systems — Medical Variants 26
Future Medical Shelter System 27
Hemorrhage Control Dressing 27
Hemostatic Dressing 28
Non-Contact Respiration Monitor 28
One-Handed Tourniquet 29
Rotary Valve Pressure Swing Adsorption Oxygen Generator 29
Special Medical Emergency Evacuation Device 30
Stryker Medical Evacuation Vehicle 31
Thawed Blood Processing System 31
Ventilatory Assist Device 31

Industrial Services Branch 32

Introduction 32

Military Relevance 32
Submersible Bio-monitoring System 33

Pharmaceutical Systems 34

Introduction 34

Military Relevance 34
Adenovirus Vaccine, Types 4 and 7 34
Dengue Tetravalent Vaccine (DTV) 35
Hepatitis E Virus Vaccine (HEVV) 35
Human Immunodeficiency Virus (HIV) Vaccine 36
Leishmania Skin Test 36
Topical Antileishmanial Drug, Paromomycin/Gentamicin 37
Malaria Rapid Diagnostic Device (MRDD) 38
Malaria Recombinant Vaccine With Adjuvant Combinations (RTS,S) 39
Diarrheal Diseases Vaccines 39
Combined Camouflage Face Paint (CCFP) 39
Hemoglobin-Based Oxygen Carrier (HBOC) 40
Antimalarial Drug, Tafenoquine (WR238605) 41
Tick-Borne Encephalitis Virus Vaccine 41
Hypertonic Saline Dextran (HSD) 42
Red Blood Cells, Extended Life (RBCXL) 42
Platelet-Derived Hemostatic Agent (PDHA) 43

Commander’s Message

Associates,

On behalf of the outstanding, dedicated professionals of USAMMDA, I present the following pages describing the status of our products and services.

USAMMDA, as the Medical Materiel Development organization in the U.S. Army Medical Research and Materiel Command, has the great opportunity to bridge the effort between the tremendous research of the USAMRMC labs and the Materiel Managers of the Command to deliver needed medical products and solutions to the Soldier. This mission of developing products for the Soldier involves the coordination with many partners, both inside the Army Medical Department and throughout the Department of Defense and beyond, with domestic and international collaborators from industry, academia, and respective governmental organizations.

The products developed include vaccines, drugs, diagnostics, and medical devices in the areas of combat casualty care, infectious diseases, and military operational medicine. The services provided by USAMMDA include the resource management component, the intensive regulatory affairs task, and the coordination of medical affairs support for products from the tech base through advanced development and on to post-marketing surveillance.

We look forward to continuing and further developing our many collaborative efforts. Please visit our website at www.usammda.army.mil and feel free to contact us as needed to understand how we can work with you in the future.

Jerome F. Pierson, R.Ph., Ph.D.
Colonel, Medical Service Corps
Commander

Our Mission

To protect and preserve the lives of America's sons and daughters by developing new drugs, vaccines and medical devices that enhance readiness, ensure the provision of the highest quality medical care to Department of Defense (DoD), and maximize survival of medical casualties on the battlefield.

Our Vision

Military operations of the 21st Century will be more survivable because of USAMMDA initiatives.

- New drugs and vaccines that we developed will protect our personnel from the threats of infectious disease and chemical attack.
- Casualties will be evacuated in vehicles we developed.
- Our combat casualty care products will enhance far-forward medical care.

Lives that otherwise would be lost, will be saved because of the vision and dedication of USAMMDA employees.

Our Personnel

The USAMMDA faced numerous major personnel changes during this year. Our Deputy Commander's term came to an end with her PCS, and in September we accomplished the 8th USAMMDA Change of Command with a fond farewell to COL Jeffrey A. Gere and a hearty welcome to incoming Commander, COL Jerome F. Pierson. The Deputy Commander position was then converted to an Executive Officer (XO) position, welcoming the first ever XO to USAMMDA, MAJ Rosemarie Kirzner. Several civilian employees retired during this year.

Matrix support has continued to be provided to other organizations through a Memorandum of Agreement between U.S. Army Medical Research and Materiel Command (USAMRMC) and the parent organizations. This includes five civilians to the Joint Vaccine Acquisition Program (JVAP), one civilian and two officers to the MC-4, Enterprise Information Systems, two officers to the Telemedicine and Advanced Technology Research Center (TATRC), and three civilians to the USAMRMC.

The following table presents a comparison between 2003 and 2004 personnel strength. Overall, USAMMDA strength continues to vary between 60 and 65.

2002 PERSONNEL PROFILE

Required	Authorized	Actual
72	39	62

2003 PERSONNEL PROFILE

Required	Authorized	Actual
75	38	56

STRENGTH: AS OF 31 DECEMBER 2003

	Military	Civilian	Contractors	Total
Required	18	47	10	75
Authorized	11	27	0	38
Actual	17	34	5	56

STRENGTH: AS OF 31 DECEMBER 2004

	Military	Civilian	Contractors	Total
Required	18	46	10	74
Authorized	11	27	0	38
Actual	16	38	11	65

Administrative Services Office

Fiscal 2004 Performance

In-House: In FY04, USAMMDA's in-house fiscal execution of direct core funds exceeded the USAMRMC disbursement target by 13 percent. However, obligations fell nine percent below the target. The FY04 in-house total direct funds also included tech base funds ($67K) received for quality assurance monitoring, Congressional funds ($12.6M), and Defense Health Program (DHP) funds ($1.3M) for HIV, Adenovirus, Anthrax, Flu Vaccine, and Force Health Protection-Investigational New Drug (FHP-IND) support.

In-House (Core-Direct)

	Allotment	Obligations	Disbursements
Fiscal 2004 Dollars ($000)	4773	4100	3271
Target (%)		95	56
Actual (%)		86	69

In addition, USAMMDA in-house managed $2.7M in reimbursable funds in FY04. This included funds from the Chemical Biological Medical Systems (CBMS) and PM-MC4 offices for matrix support personnel. Reimbursable funds were also received from the Marine Corps, Kuwait, Canada, and from U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), U.S. Army Center for Environmental Health Reserach (USACEHR), U.S. Army Medical Materiel Agency (USAMMA), and Walter Reed Army Institute of Research (WRAIR) for various task order services.

Program Wide: The laboratory programs exceeded the FY04 obligation target by 5 percent, and the disbursement target by 19 percent. Obligations and disbursements for the extramural programs fell below the established targets by 1 and 25 percent, respectively. Performance in the total command-wide development program met the obligation target, and fell 11 percent below the disbursement target. In addition, FY04 total program direct funds reflect a $12M increase from FY03 funding. Fiscal execution performance at the project level is provided on the next page.

Program-Wide (Core-Direct)

	Allotment	Obligations	Disbursements
Fiscal 2004 Dollars ($000)	24,286	22,541	12,767
Target (%)		95	56
Actual (%)		93	53

In FY04, USAMMDA managed a total of $21.8M of Congressional funds. The FY04 Congressional funds were received for Portable Digital X-Ray, LSTAT, Chitosan Hemorrhage Control Dressings, Automated Laboratories for Biodefense, Cartledge Infuser, Pressure Swing Adsorption Oxygen Concentrator, and Hemoglobin Based Oxygen Carrier (HBOC). In total, including direct, reimbursable, and Congressional funding, USAMMDA managed $50.3M of funds in FY04.

Fiscal 2004 Program Execution

DIRECT – ADVANCED DEVELOPMENT									
		PERCENT							
	Allotment	**In-House**		**Lab**		**Extramural**		**Total**	
Project	**($000)**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**
808	5383	99	92	100	80	99	49	99	65
811	132	98	86	0	0	100	2	99	58
836	4106	94	86	98	73	100	59	98	69
837	1088	100	49	100	60	98	60	100	57
Total 6.4	**10,709**	**97**	**84**	**100**	**74**	**99**	**53**	**99**	**66**
812	3119	100	84	100	81	99	1	100	66
832	5506	64	49	0	0	100	37	90	40
834	1249	100	81	100	68	100	27	100	59
849	3703	92	54	100	89	65	7	72	20
Total 6.5	**13,577**	**78**	**58**	**100**	**79**	**87**	**23**	**88**	**42**
Total Adv Dev	**24,286**	**86**	**69**	**100**	**76**	**92**	**35**	**93**	**53**
Tech Base	67	21	7	0	0	0	0	21	7
DHP	1334	100	73	0	0	0	0	100	73
Congressional	21851	99	40	100	52	96	26	98	35
Total Direct	**47,538**	**95**	**50**	**100**	**75**	**94**	**31**	**95**	**45**
REIMBURSABLE									
		PERCENT							
	Allotment	**In-House**		**Lab**		**Extramural**		**Total**	
Project	**($000)**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**
CBMS	1984	98	46	0	0	0	0	98	46
Other Reimb	746	99	78	0	0	0	0	99	76
Total Reimb.	**2730**	**98**	**55**	**0**	**0**	**0**	**0**	**98**	**55**
TOTAL PROGRAM MANAGED									
		PERCENT							
	Allotment	**In-House**		**Lab**		**Extramural**		**Total**	
Project	**($000)**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**	**OBL**	**DISB**
Total Program	**50,268**	**96**	**50**	**100**	**75**	**94**	**31**	**95**	**45**

Computer Support

The year 2004 was busy for the Computer Support staff. In addition to the significant routine tasks associated with maintaining USAMMDA IT resources, we responded to several major events by implementing significant changes and upgrades.

In March of 2004, USAMMDA joined USAMRMC and the Medical Command (MEDCOM) in the migration to Microsoft Active Directory. For USAMMDA, this meant upgrading to Windows 2003 Enterprise Server and consolidating our four servers which comprised the USAMMDA Windows NT 4.0 Domain to three Member file and print servers in the AMED Domain. We upgraded hardware to Dell PowerEdge 2600 servers with Integrated RAID systems.

Preparation for Active Directory included changing all Internet Protocol (IP) addresses from "Army IP Space" to "MEDCOM IP Space." The USAMMDA received new IP subnets which required us to reassign addresses to all USAMMDA resources. Additionally, to accommodate the new email configuration, USAMMDA upgraded to Microsoft Office 2003 to take advantage of the cache mode for Outlook.

Migration to Active Directory commenced with user account migrations in April. The first of the three USAMMDA Organizational Unit (OU) servers was placed in use in May 2004 and the third was activated in August. During this period, USAMMDA workstations and printers were migrated into the AMED domain. The old NT 4 USAMMDA Domain was terminated on September 3, 2004. The USAMMDA contracted with the Telos XACTA Company to complete the DITSCAP accreditation process and evolve it into a more automated process. On October 31, 2004, COL Jerome F. Pierson, as USAMMDA Designated Approval Authority (DAA), approved the accreditation for the USAMMDA LAN.

In the fall of 2004, USAMMDA Computer Support began development of a security profile for Windows XP Professional and the subsequent migration from Windows 2000 Professional workstations to Windows XP Professional. To facilitate this migration, and more importantly, to standardize the installation of workstation software, we purchased Symantec Ghost software.

We completed implementation of the Quality Assurance (QA) Checklist database and placed it in use for monitoring clinical trials. We began analysis for a redesign of the Product Tracking System (PTS) in response to a reorganization of USAMMDA finances.

In October we began integration of the Regulatory Affairs groups from USAMRMC and USAMRIID, increasing our user base from nominally 50 to nominally 70. Computer Support issues include IP addressing, equipment standardization, resource sharing and user support. This effort continues into 2005.

Medical Affairs Division

Force Health Protection Branch

Introduction

In 2002, USAMMDA assumed the role as the executive agent for the management of the DoD's Force Health Protection program. In February 2004, USAMMDA established a Force Health Protection (FHP) Office to plan, implement, and sustain DoD directed FHP-IND* protocols and to train the investigational staff in the execution of these protocols according to the U.S. Food and Drug Administration (FDA) regulatory guidelines. The FHP office currently has four product managers overseeing 10 IND protocols who coordinate the myriad of administrative, clinical and regulatory activities needed to successfully activate and sustain these protocols worldwide.

Military Relevance

Military personnel deployed in particular military operations could potentially be exposed to a range of chemical, biological, and radiological weapons as well as diseases endemic to an area of operations. Force Health Protection is an organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions. It is DoD policy that personnel carrying out military operations shall be provided the best possible FHP, including safe and effective medical countermeasures to chemical, biological or radiological warfare and endemic disease threats. The FHP office manages those medical countermeasures. Current medical countermeasures include FHP products for the prophylaxis or treatment of Smallpox and the complications from severe reactions to smallpox vaccine, anthrax, botulism, Crimean-Congo hemorrhagic fever, Lassa fever, Leishmaniasis, and Korean hemorrhagic fever. The FHP IND protocols are listed in the table on the following page:

IND No	Title
65480	Department of Defense Protocol for the Use of Cidofovir (VISTIDE®) as a Treatment for Adverse Reactions Associated with Vaccinia Virus Vaccination
65480	Department of Defense Contingency Protocol for Emergency Use of Cidofovir (VISTIDE®) as a Treatment for Smallpox
8429	Protocol for the Administration of Vaccinia Immune Globulin Intramuscular (Human) to Subjects Who Experience Complications Resulting from Vaccination with Vaccinia Virus
10999	Protocol for the Intravenous Administration of Vaccinia Immune Globulin (Human) Liquid Formulation to Treat Complications from Vaccination with or Accidental Exposure to Vaccinia Virus
BB-IND 3723	Protocol for Vaccination of Selected Volunteers with Pentavalent Botulinum Toxoid to Protect against Botulinum A Toxin Toxicity
BB-10,621	Emergency Use of Investigational Heptavalent Equine-Based Botulinum Antitoxin (Types A, B, C, D, E, F, and G) After Exposure to Clostridium botulinum or Other Closely Related Bacterial Species
BB-IND 10081	Contingency Protocol for Anthrax Vaccination to Protect against Bacillus anthracis Spores

Accomplishments

Emergency Use Authorization

BioShield provisions of the 2004 National Defense Authorization Act identified procedures for the use of an Emergency Use Authorization (EUA) that allows DoD to request use of a non-FDA approved product (investigational product) in the event of a national emergency. The FHP office under the BioShield provision collaborated with the Centers for Disease Control (CDC) in the submission to the FDA the necessary documents to allow for the activation of an EUA for “The Use of Aventis Pasteur Smallpox Vaccine (APVS) 1:5 Dilution in the Vaccination of Individuals after Exposure to Variola Virus Due to a Bioterrorism Incident or Public Health Emergency” in the event of a national emergency. Also, FHP collaborated with the CDC in the writing of the Anthrax Vaccine Adsorbed document to allow for the submission of an EUA entitled, “Request For Emergency Use Authorization For The Use Of The Anthrax Vaccine Adsorbed (AVA, BioThrax ™) To Protect Individuals After Potential or Confirmed Exposure to Anthrax Spores.”

Force Health Protection Related Accomplishments

During the calendar year 2004, the FHP office was actively involved in the writing of FHP IND protocols, establishing new sites, activating and sustaining these protocols in accordance with strict regulatory guidelines worldwide.

OCONUS:

The FHP office established FHP-IND protocols at Landstuhl Regional Medical Center, Germany, and the121st General Hospital, Seoul Korea, with the capability to administer, under IND, the FHP-IND (investigational) products necessary to treat Botulism, Korean hemorrhagic fever (KHF), Lassa fever, Crimean-Congo Hemorrhagic fever and smallpox disease or the complications from severe reaction to smallpox vaccine. As part of their regulatory activities, the FHP office provided continuous regulatory support for all of the FHP-IND protocols including continuing review and required periodic reports to the FDA, receipt and processing of FHP-IND products and data from sites where these products are located. Because of the potential for a Mass Casualty (MASCAL) involving hundreds of patients and recognizing that medical facilities in U. S. Forces Korea (USFK) Area of Responsibility (AOR) would not have the extensive supplies needed to administer botulinum antitoxin the FHP office coordinated with U.S. Army Medical Materiel Center, Europe (USAMMCE) and 16th Medical Logistics (MEDLOG), Korea for the delivery of 200 individual “BOT” kits from Germany to Korea, each containing sufficient supplies and pharmaceuticals to support administration of botulinum antitoxin to one person. Being acutely aware of the logistical trail associated with any investigational product, the FHP office co-authored, coordinated and established a Memorandum of Agreement with USAMMCE and 16th MEDLOG, Korea, to coordinate medical logistics activities in support of FHP contingency protocols in their respective AOR.

CONUS:

Recognizing the need to gain efficiencies in the execution of the Pentostam protocol, the FHP office wrote the new streamlined Pentostam protocol for use at Walter Reed Army Medical Center (WRAMC) and Brook Army Medical Center (BAMC) to support the investigational use of Pentostam in the treatment of cutaneous Leishmaniasis for Servicemembers returning from the Central Command (CENTCOM) AOR. The FHP office also collaborated with the DoD Military Vaccine Agency (MILVAX) program in negotiating and awarding a contract to Logistics Health Incorporated (LHI) to develop and maintain a readiness capability to deploy a team of nurses, nurse coordinator and physician worldwide to augment the execution of FHP

contingency protocols. On the direction of the Army Surgeon General; USAMMDA's FHP office collaborated with WRAMC personnel and provided regulatory affairs expertise, manpower, administrative and logistical support to the short noticed Surgeon General directed one-half dose influenza vaccine study conducted at the Pentagon and WRAMC.

Educational Training and Regulatory Affairs Activities

As part of their overall educational and training strategy, the FHP office planned and deployed a team of six members to provide a four-day FHP training course to the 121st General Hospital organic assets to enhance their ability to administer FHP-IND products in compliance with FDA regulatory guidance. Future similar educational programs are planned for personnel at the Landstuhl Regional Medical Center, Germany and Tripler Army Medical Center, Hawaii.

The FHP office leverages technologies by collaborating with EduNeering in the creation of a new "web-based" Good Clinical Practices (GCP) training course to assist FHP IND protocol principal investigators and clinical associates in fulfilling their FDA regulated GCP training requirements. This effort had a two-fold impact: 1) providing the required training to FHP personnel in a timely and efficient manner and 2) it will save the MEDCOM thousands of dollars in TDY costs usually incurred when personnel have to travel (OCONUS and CONUS) to attend civilian GCP training programs.

Finally, the FHP office provided proactive leadership by coordinating and directing the quarterly meetings for the DoD's Force Health Protection IND Steering Committee.

* Investigational New Drug (IND): Any drug or vaccine (collectively termed "drug") which is unapproved (by FDA) for its current indication. Classically, a drug is in IND status while it is under development (pre-FDA approval) but must be used in humans to demonstrate its safety and efficacy to the FDA. A drug may remain in IND status if its safety profile makes it acceptable for use in humans but the disease (e.g. ,botulism) precludes conducting efficacy studies to show that it works in humans (unethical to expose humans to live botulism). When a drug is in IND status, even if used for Force Health Protection, it must be administered under an approved protocol, just like it was being used in a clinical study, and extensive documentation of all aspects of "the study" must be kept, including custody of the drug, qualification of participants, informed consent, administration of the drug, adverse reactions, scheduled follow-up of participants, disposition of the subject, disposition of the drug. This is difficult and labor intensive under normal circumstances in controlled conditions (i.e., research clinical study). On the battlefield, the challenges are magnified astronomically.

Regulatory Affairs Division

Introduction

On 29 September 2004, USAMMDA assumed the mission for Regulatory Affairs (RA) leadership, policy and coordination for the USAMRMC. In support of this new responsibility, an RA Division was created within USAMMDA. The RA organization was originally staffed with the USAMMDA Clinical Trial Branch (CTB), along with representation from the RA Branch of USAMRMC's Deputy for Regulatory Compliance and Quality. Regulatory Affairs staff from USAMRIID was integrated on a detail basis with Dr. Judy Pace-Templeton identified as the overall RA Director for USAMRMC RA (effective in 2005). The mission of RA is to develop regulatory strategies, policies, guidance documents, training programs and regulatory cost models to facilitate a common understanding and execution of FDA regulated research throughout USAMRMC. Additionally, the RA Division was expanding in order to be capable of regulatory writing, clinical trial data management, and planning of product testing. The USAMMDA RA Division is staffed (through assignment and detail) by 25 civilians and contractors (includes clinical monitoring) who are responsible for the maintenance and direction of approximately 48 investigational products, 6 licensed products and 12 master files.

Military Relevance

Military personnel are deployed worldwide and may be exposed to a variety of endemic diseases as well as chemical and biological warfare agents. In many cases, there are no licensed products available for use against these agents and new products must be developed. The RA Division supports the development of new products through coordination of the regulatory strategy to obtain FDA approval for new products and ensuring the regulatory compliance of these products as they advance through the development cycle.

Accomplishments (Includes RA activities as part of RCQ)

In January 2004, Ms. Kathie Mantine, LTC Ann Altman, and COL Jerry Pierson coordinated a meeting between USAMRMC RA, Quality Assurance (QA), Human Subjects Protection and product management with the regulatory teams from the National Institute of Health/ National Institute of Allergy and Infectious Diseases/Division of AIDS (NIH/NIAID/DAIDS) to discuss common approaches to the management of the HVTN044 and ESPRIT.

Also in January, COL Pierson participated in a joint/combined conference between USAMRMC, other DoD and governmental organizations and the Medical Research Institute of India in Bangalore, India. COL Pierson presented on processes required by the U.S. FDA for Investigational New Drug studies.

In April, Ms. Mantine was awarded Regulatory Affairs Certification by the Regulatory Affairs Professional Society.

COL Pierson participated from Bangkok along with the Armed Forces Research Institute of Medical Sciences (AFRIMS) Retrovirology staff and the Thai Ministry of Public Health staff in the charter meeting of the Data and Safety Monitoring Board (DSMB) meeting for the Phase 3 HIV vaccine trial. his initial meeting was conducted by telecon with Kathie Mantine and John McNeil serving as U.S. host site. In July 2004, COL Pierson and Ms. Mantine participated in an on-site DSMB meeting conducted in Bangkok and Rayong Province that allowed for all DSMB members to receive briefings from the sponsor organization, the investigators, and to receive tours of a screening site, clinical trial site, the vaccine storage site, and the laboratory specimen receipt and processing center. In September, COL Pierson and Ms. Mantine participated in an FDA Biologics and Vaccine Products Advisory Committee meeting along with representatives from WRAIR Retro, AFRIMS Retro, NIAID/DAIDS, and the Thai Ministry of Public Health to present the Phase 3 HIV vaccine trial. Ms. Mantine also established a monthly sponsor's responsibilities and oversight committee plus provided support to regular pharmacovigilance meetings in order to work through issues identified in the conduct of the HIV vaccine trial.

COL Pierson presented the requirements for using investigational products for force health protection to the Combatant Command Surgeons Conference in May 2004.

Ms. Mantine coordinated the availability of regulatory affairs training via teleconference/webcast throughout the year. Additionally, the RA staff planned and conducted a USAMRMC-wide 3-day training program in September 2004 for over 200 investigators, product managers, monitors, and RA staff. In December 2004, Ms. Mantine coordinated the presentation of a combined training program for USAMMDA product managers and regulatory staff involving presentations from FDA staff as well as USAMMDA RA and PM staff.

COL Pierson, COL Gere, LTC Altman, and Dr. Pace took part in the USAMRMC Regulated Activities Re-Engineering workgroup between January 2004 and May 2004.

Ms. Mantine and COL Pierson took part in the FDA Decision Gate working group process between June and December 2004.

COL Pierson, LTC Altman, and the staffs of Clinical Trial Monitoring (CTM) and FHP supported the execution of a clinical trial of the flu vaccine involving over 1300 participants. Ms. Shirley Roach of CTM played a key role in serving as

clinical research coordinator for the study conducted by physicians from the Walter Reed Army Medical Center Department of Allergy-Immunology.

The RA staff provided regular support to the Integrated Product Teams for adenovirus vaccine, hemoglobin based oxygen carrier, physiologic status monitor, and paramomycin/gentamicin. COL Pierson also assisted the Combat Casualty Care Research Area Directorate in the identification of regulatory options for the use of recombinant Factor VIIa for management of severe bleeding.

Quality Assurance/Clinical Trial Monitoring Branch

Introduction

The USAMMDA's mission is to develop new drugs, vaccines and medical devices to protect and preserve the lives of servicemen and women. The safety and efficacy of many of these products are tested using IND applications. As a sponsor of record for clinical trials, USAMMDA is responsible for ensuring that clinical studies are conducted in compliance with appropriate regulatory requirements. This is accomplished through clinical monitoring performed by the CTM Branch. Monitors participate in site selection, site preparation, training of site personnel regarding the trial, site monitoring and follow-up to ensure compliance. Monitors also participate in evaluation of manufacturing compliance of the test article used in clinical trials. Monitoring visits to the clinical sites, pharmacies and laboratories assure the integrity of clinical data with respect to accuracy, accountability, documentation, and procedures. Integrity is assured through review of case report forms, source documents, medical records, and regulatory documents in comparison to protocol requirements.

Staffing

The CTM Branch is under the leadership of LTC Ann Altman. With two new monitors and one administrative assistant hired in 2004, the total staff is now seven. One of the newly hired monitors is a registered nurse (R.N.) with certifications in Institutional Review Board (IRB) management and as a Clinical Research Professional (CRP). The other is a retired scientist with hospital and vaccine production experience, and is board certified in Public Health Microbiology and Clinical Microbiology. One CTM monitor was promoted to a Regulatory Affairs Specialist position within CTM.

Tasks

Monitoring Special Immunization Program (SIP) Protocols at USAMRIID

The SIP Clinic supports USAMRIID and extramural sites that administer vaccines to provide an added layer of protection beyond standard safety procedures to designated laboratory personnel at risk of exposure to various pathogens and toxins. Studies of vaccines which remain under IND status are monitored by CTM. In 2004, six INDs with eight protocols having an average of 200 subjects per protocol were monitored. Monitoring included the review of 231 case report forms, four Regulatory File reviews, one Close Out visit, and one Study Initiation.

CTM collaborated with USAMRIID Research Serology Laboratory to develop a validation protocol for the PRNT (Plaque Reduction Neutralization Test) assay, results of which are essential in determining efficacy of various SIP vaccines. A validation protocol was drafted and an Analysis of Variance (ANOVA) is being performed on retrospective data to establish validation of the assay.

Establish and Monitor Regulatory Files for Force Health Protection Contingency Protocols

The USAMMDA Force Health Protection assists the Secretary, DoD by providing a coordinated program for maintaining the availability of IND products both in times of peace and in war. The CTM Branch monitors these IND protocols for compliance. Along with monitoring, CTM assisted with preparing regulatory files for investigational products which may be used to protect the health of the deployed Force. The CTM Branch also provided oversight and instruction for maintenance of these regulatory files at both domestic and international locations. Monitoring activities for FHP in 2004 included 8 regulatory file reviews at 3 overseas sites and 10 regulatory file reviews at 4 domestic sites.

The CTM Branch was a major player in the treatment of Leishmaniasis via protocols and has monitored a protocol for treatment of Leishmaniasis with Pentostam for a number of years with minimal enrollment. With Operation Enduring Freedom, however, there was a dramatic increase in the number of Soldiers requiring treatment for Leishmaniasis. Although some of these Soldiers were enrolled in the existing clinical trial with Pentostam, there was also the need to establish additional sites and to develop a treatment protocol. The CTM Branch participated in the writing of the streamlined protocol and in establishment of additional sites, as well as the monitoring of these sites once the protocol was implemented.

Simultaneously, an alternative treatment using an approved heat treatment device was studied to compare the effects of heat treatment with Pentostam. The advantage of the heat treatment protocol is that it does not require evacuation of the infected patient from the area of operation, as is the case with Pentostam. This past year, CTM was engaged in protocol development, site initiation and trial monitoring for the heat treatment protocol.

Monitoring of Protocols not SIP or Contingency

There are numerous Phase 1, 2 and 3 studies initiated or continued this year. In addition, a number of protocols were prepared for future implementation. To address the monitoring needs of these studies, CTM completed 21domestic visits

and 18 international visits throughout the year.

On the domestic visits, a Tafenoquine protocol active at Uniformed Services University of the Health Sciences (USUHS) received four monitor reviews this past year, while one protocol for Leishmania at WRAMC was monitored five times. Monitoring at WRAIR involved three reviews of HIV protocol #11905, five reviews of malaria protocol #12227, and four reviews of Dengue protocol #11990.

Clinical trial monitors traveled internationally to eight countries in oversight of 10 protocols for HIV, Dengue, Malaria, and Tefenoquine, Riboviran, and Hepatitis E. Eighteen reviews of 10 protocols occurred. Of these 10 protocols reviewed, two were monitored by contract research organizations (CROs). The CTM Branch monitoring expanded to involve utilization of other pharmaceutical monitors and contract monitors due to an increase in workload. Consequently, in addition to monitoring, the CTM Branch performs contract compliance audits for those monitors contracted.

External Collaboration:

The CTM Branch developed six Command policies in collaboration with the Command's Quality Assurance office. These policies were approved and made final in April 2005.

Special Tasks

Influenza (Flu) Vaccine Clinical Trial

The CTM Branch took the lead in coordinating and conducting an influenza vaccine clinical trial with Ms. Shirley Roach, a Clinical Trail Monitor, performing the functions of the Clinical Trial Coordinator. Approximately 1300 subjects were recruited and consented. With the potential shortfall of Influenza vaccine in 2004, a study was designed to determine if the immune response of the ½ dose of flu vaccine is non-inferior to that of a full dose. This plan built on the results of a previous flu dose study**,** (Treanor, J. et.al. *Evaluation of a Single Dose of Half Strength Inactivated Influenza Vaccine in Healthy Adults.* Vaccine. Vol. 20, Issues 7-8, 15 Jan. 2002, pp. 1099-1105.) The FDA required the study be conducted under an investigational new drug (IND) application. This study was a joint venture with MILVAX, CDC, NIAID, USAMRIID, WRAMC and WRAIR. The USAMMDA was tasked to conduct the study in compliance with regulatory guidelines.

A USAMMDA team to include CTM staff coordinated resources for the study. CTM managed study coordination and site initiation at the Pentagon and WRAMC. The active portion of the study ran from 25 October to 20 December 2004.

Training developed within CTM was presented to study staff at WRAMC, WRAIR, USAMRIID and independent contractors by Ms. Roach. A database was created to allow secure entry in real time of demographic information for study participants. The results of the study and the unblinding of the dose codes are not yet known. Since CTM conducted the study, a contract was established with Clinical Research Management (CRM), Inc., to perform the monitoring of the study.

Service on HSRRB:

LTC Ann Altman served on the Human Subject Research Review Board (HSRRB) during 2004, applying her nursing expertise to the review of protocols for human subject protection issues. As a member of the HSRRB, proficiency is required in the review of DoD and Congressionally Directed Medical Research Program (CDMRP). These greater than minimal risk protocols are diverse and require in-depth assessment to adequately address potential problems and pitfalls

Applied Medical Systems Project Management Division

Introduction

The Applied Medical Systems Project Management Division (AMSPMD) is a multidisciplinary team with broad mission capabilities for the advanced development of medical products used to sustain and support the warfighter. The team consists of both product managers and model makers, who have expertise in project management, engineering, fabrication, and technical testing. The product managers analyze functional requirements, conduct market investigations, and develop and execute technical and program strategies and plans for all acquisition program phases from pre-Milestone A through Full Rate Production.

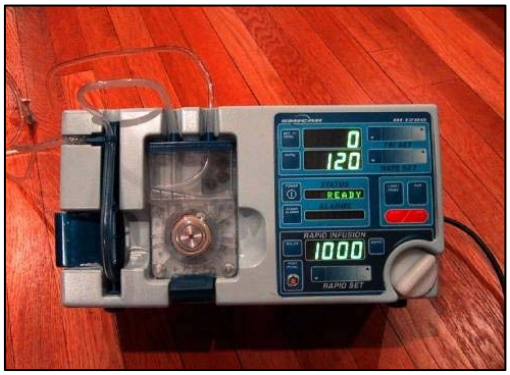
The product managers also direct program resources, and defend program content and structure during science and acquisition forums. The focus for the Division is an early involvement with products that are within the technology base, resulting in streamlined development efforts by combining Milestones and transitioning medical products rapidly to the logistician for procurement and fielding. As a result of this emphasis, product managers are busy with many products either developing and executing broad acquisition strategies or monitoring technology base research efforts. Examples of active products include: Ceramic Oxygen Generator; Dental Field Treatment and Operating System; Future Medical Shelter System; Future Combat Systems – Medical Variants; Hemostatic Dressing; Rotary Valve Pressure Swing Adsorption Oxygen Generator;

Ventilatory Assist Device; Thawed Blood Processing System; and One-Handed Tourniquet.

Military Relevance

The AMSPMD designs, develops, and tests field medical equipment in support of battlefield combat casualties. The AMSPMD specializes in developing new and innovative breakthrough technology as well as adapting and hardening commercial-off-the-shelf (COTS) systems for joint military applications. For example, AMSPMD personnel were intimately involved with the development of the Special Medical Emergency Evacuation Device (SMEED). More than 300 SMEED systems were deployed with Army, Marine, and Air Force units in support of Operations Enduring (OE) and Iraqi Freedom (OIF).

Cartledge Infuser



The Cartledge Infuser (CI) is intended to allow a physician to normalize a patient's hemodynamic status. The CI is a variable rate infusion pump that allows a physician to replace blood volume at flow rates ranging from 20 ml per hour through 1200 ml per minute. A blood warming system is incorporated into the design and provides optimal blood warming at any flow rate. The CI operates on standard alternating electrical power, and is capable of battery operation for up to one hour. It weighs approximately 18 pounds, and is 14 inches wide, 8 inches high, and 8 inches deep.

Design efforts are ongoing, and Smisson-Cartledge, the contractor, selected Spartan, Inc., of Deland, FL, to finalize the design and produce the prototype system. Smisson-Cartledge is currently building prototype systems and preparing its 510(k) application.

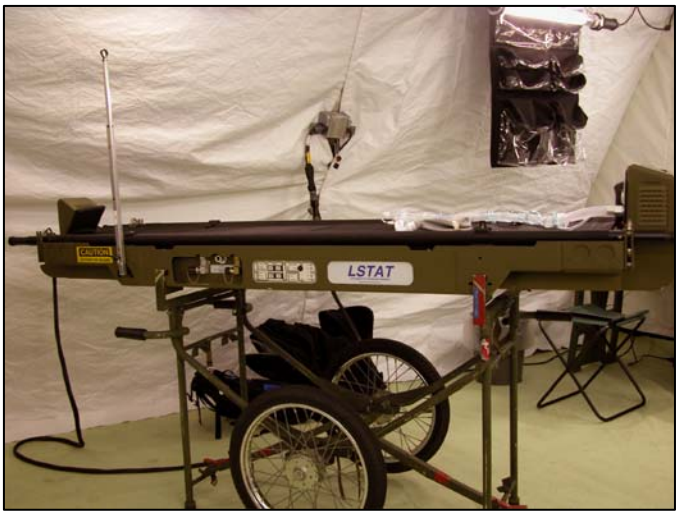
Ceramic Oxygen Generator

The Ceramic Oxygen Generator (COG) project is developing leading edge technology for the production of high purity, medical grade oxygen. This type of oxygen generator has an advantage over conventional methods such as pressure swing adsorption by generating very high purity oxygen without using any moving parts. This system uses a metal/ceramic membrane matrix to avoid the cracking and sealing problems that have been experienced by other developers attempting to commercialize COGs.

Improvements made this past year to the cell materials have produced cells that generate high purity oxygen with long stable operating performance. The development effort is currently centered on the production of a prototype portable oxygen generator. New cells with two active surfaces per cell have been tested and have worked without problems. This design has cut the size and weight of the oxygen generator in half.

Critical Care System for Trauma and Transport

The requirement for a Critical Care System for Trauma and Transport (CSTAT) describes a single-patient, intensive care capability that will be used to maintain life support and stabilization of battlefield casualties during evacuation. The CSTAT requires incorporation of a defibrillator, ventilator, vital signs monitor, infusion pumps for fluid resuscitation and administration of medications, suction unit, and self-contained oxygen supply in a unit that attaches to a standard North Atlantic Treaty Organization (NATO) litter.



The Life Support for Trauma and Transport (LSTAT), which was cleared for marketing by the FDA, satisfies the majority of the CSTAT requirements. he contractor is currently modifying the LSTAT to fully satisfy those requirements. These modifications will lead to two completely new configurations: 1) a Next Generation LSTAT weighing roughly

half as much as the current system, and 2) an LSTAT-Lite, which will have somewhat reduced functionality, but will only weigh about 40 pounds.

There are currently 42 fully functional LSTAT systems in the inventory, 12 of which are the most recent Model C LSTATs. The LSTAT Model C includes an upgraded vital signs monitor, infusion pump, and biphasic defibrillator. Like the Model B, the LSTAT Model C was given a fleet wide airworthiness release by the U.S. Army Aviation and Missile Command for use on all UH-60 helicopters, and it was given Air Force clearance for use on KC-135 fixed-wing aircraft.

The White House Medical Unit continued to employ LSTAT systems in its operations. The LSTAT systems were also deployed with both Army and Navy units in support of Operations Enduring and Iraqi Freedom. The 52nd Medical Battalion evaluated LSTAT systems in casualty evacuation and battalion aid station operations during a field exercise in Korea.

Dental Field Treatment and Operating System

The Dental Field Treatment and Operating System (DEFTOS) incorporates the latest technology to provide a modern, lightweight dental system for field operations. It reduces the need for compressed air and thus large power generator capacity in the field. The unit incorporates an electric hand piece, which produces superior torque compared to previous systems.

During CY04, a contract was let to procure the DEFTOS for fielding. Development of a portable training package was initiated and First Article Testing of ten production units was started.

Field Sterilizer Improvement Device

The field sterilizer currently in use is a well-proven piece of equipment. One of the shortcomings has been its high water consumption; it uses 2.5 gallons of water every time it sterilizes a load of materials. A water recovery device was developed before Operation Desert Storm (ODS). To meet the immediate need, the prototype was put into production before completely optimizing the design. The manufacturer of the ODS-designed water recovery system designed an improved version. The new version will need testing to verify its performance and ruggedness.

This project is being coordinated with USAMMA, as well as the combat developer, who has written the ORD and sent it to Training and Doctrine Command (TRADOC) for approval. The current plan is to incorporate the Field Sterilizer Improvement Device (FSID) into the new hospital sets as they are built at the depot; the FSID would be added to the Unit Assemblage for the Central Medical Supply to equip existing hospitals.

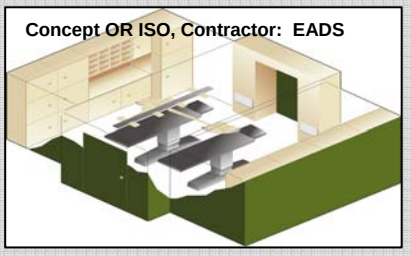
Future Combat Systems — Medical Variants

The Future Combat System (FCS) – Medical Vehicle-Evacuation (MV-E) and Medical Vehicle-Treatment (MV-T) will function as the ground medical evacuation and treatment assets in the Unit of Action. Medical capability will include an automated litter lift system, on-board oxygen generation, suction, storage space for essential medical items and equipment, automated data management, plus the capacity to carry four litter patients or six ambulatory patients and a crew of three (MV-E), or provide interior space for the treatment of two patients and a crew of four (MV-T).

Systems unique to the MV-E such as the blood refrigerator and oxygen system are now technically ready, the vehicle manufacturer and integrator have to supply their requirements to make the final engineering decisions.

The Joint Requirements Oversight Committee approved the ORD on 14 April 2003. A Milestone B review was held on 15 May 2003; the system was transitioned to the next phase of development. United Defense, the FCS vehicle manufacturer, has produced several iterations of potential designs (Design Excursions 3 and 4) and is now working on the Best Technical Approach (BTA) for vehicle design. The PM-FCS conducted a Manned Ground Vehicle (MGV) In-Process Review (IPR), and confirmed that the FCS contract does include one MV prototype to be delivered in FY08 in line with the other MGV prototypes. The ORD requirements have been reviewed and all suggested changes have been forwarded to TRADOC for inclusion in the next iteration, for anticipated issue in 4QFY04.

Future Medical Shelter System



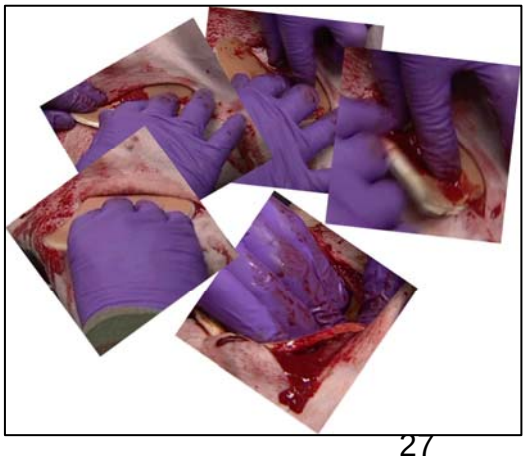
The Future Medical Shelter System (FMSS) is a multifaceted program which leverages Congressional funding to explore advanced rigid and soft-walled shelters for forward deployed healthcare providers. The objectives of the FMSS program are (1) to develop a self-contained emergency response package for use by Forward Surgical Teams (FST), and (2) to develop a replacement for the DEPMEDS operating room shelter, which has reduced weight and enhanced transportability and deployability. These efforts consist of chemically/biologically-hardened International Standards Organization (ISO) shelter with quick erect/strike times and integrated electrical, water, and medical packages, and provide 1200 square feet of soft tentage as patient care wards. Three development efforts are underway:

The first Mobile Medical International Corporation (MMIC) prototype was developed and exhibited at several conferences this year. MMIC is seeking approximately $9M in FY05 Congressional appropriations.

The company of EADS-Dornier began the development of schematic plans for a 3:1 expandable ISO shelter configured as an operating room. Insufficient funds exist for the development of airbeam tentage or fabrication of any prototypes. EADS-Dornier is seeking approximately $8M in FY05 Congressional funding.

Hemorrhage Control Dressing

The Hemorrhage Control HemCon (Chitosan) Dressing (CD) is intended to provide a revolutionary improvement in the control of severe life-threatening hemorrhage. The CD is manufactured from Chitosan; a natural biomaterial derived from shrimp shells. It is intended for use by the combat medic/combat lifesaver and other medical personnel on the battlefield.



In February 2004, the Joint Staff, Health Services Support Division, began to regulate CD distribution in theatre due to the product's limited availability. However, CD production more than doubled by the close of 2004 due to key personnel and process changes made by the manufacturer. These changes resulted in significantly increased CD production. Approximately 38,000 CDs were shipped to units in the CENTCOM AO.

In July 2004, the USAMRMC was able to provide significant financial support to the manufacturer, which will result in substantially greater CD production rates over the next two years.

Madigan Army Medical Center conducted a survey of CD users in the CENTCOM AO. There were about 45 responses, 44 of which indicated the CD worked well when used as intended.

Hemostatic Dressing

The Hemostatic Dressing (HD) is intended to provide a revolutionary improvement in the control of severe life-threatening hemorrhage. The HD is manufactured from human blood clotting proteins, fibrinogen and thrombin, obtained from expired blood plasma. It is intended for use by the combat medic/combat lifesaver and other medical personnel on the battlefield.

This product was fielded in 2003 under an FDA approved battlefield clinical protocol. The protocol was difficult to administer under battlefield conditions. The HD was used one time under this protocol to treat a Soldier with uncontrolled bleeding resulting from a gunshot wound to the thigh. The HD successfully stopped the bleeding. The principal investigator withdrew the protocol when the Chitosan Dressing became more widely available. The final clinical study report is in preparation.

The USAMRMC's contract with the IND holder and manufacturer was closed out in 2004. However, USAMRMC continues to hold a high level of interest in this technology.

Non-Contact Respiration Monitor

The Non-Contact Respiration Monitor (NCRM) is a device for use by the medic to monitor the respiration of Soldiers at a distance in Military Operational Protective Posture (MOPP) gear. It can be attached to a gas mask filter canister, or incorporated into the filter canister or gas mask. It senses the flow of air entering the gas mask filter canister, and can cause red or green light-emitting diodes to blink, set off other alarm

mechanisms, or telemeter data, as required, to signal the state of casualty breathing. This will be a new capability for the medic that will be particularly useful for triage in mass casualty nuclear, biological, and chemical environments. It will be lightweight, totally self-contained, and reliable in high noise and vibration environments such as medical evacuation helicopters.

The NCRM provisional patent, filed on 10 September 2003, was assigned patent number 60/501,403. It was subsequently advertised in the Federal Register on 9 January 2004. A second-generation prototype was designed and built with all components, including a refined sensor, contained in one structure. Testing of the sensor operation showed high reliability. A utility patent application was submitted to the U.S. Patent and Trademark Office.

One-Handed Tourniquet

The One-Handed Tourniquet (OHT) is being designed to enable a severely wounded casualty to stop his or her own flow of blood in the field when assistance is not available. The plan for the OHT is to eventually be issued to individual Soldiers. Initially, to expedite the availability of the OHT, the AMEDD Center and School decided that each Combat Medic (91 W) would be provided three and each Combat Lifesaver would be provided two. A transportable training package has been developed. A Market Investigation of commercial units uncovered alternative units which were extensively evaluated. One unit (Combat Application Tourniquet (CAT)) was selected and recommended for fielding.

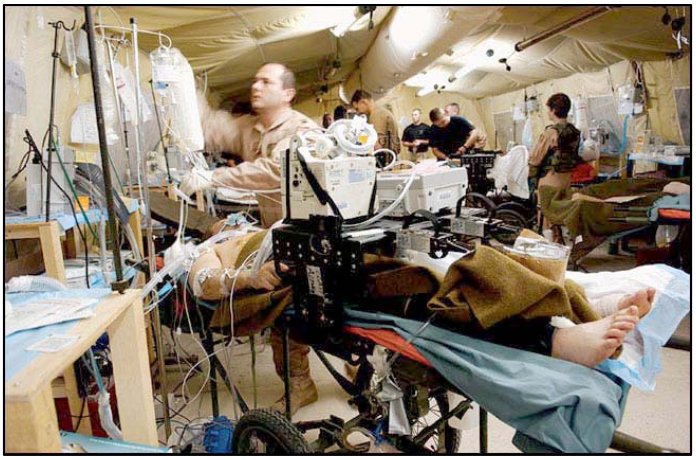
Rotary Valve Pressure Swing Adsorption Oxygen Generator

The Rotary Valve Pressure Swing Oxygen Adsorption Generator (RVPSOAG) is designed to replace the “D” cylinder for patient care and transport. The RVPSOAG is a substantial simplification of existing pressure swing adsorption oxygen generator technology. The use of a rotary valve, driven directly by a small motor, eliminates complex valve and control systems used in conventional oxygen generators. Taking advantage of the reduced

complexity reduces the weight and size of the oxygen generator and increases the efficiency of the generation process. This project will develop a portable device to meet the combat developer's requirements for a portable point-of-use oxygen generator.

The RVPSOG manufacturer built and delivered two different types of prototypes. The first prototype uses a reciprocating air compressor, weighs about 14 pounds, and uses standard lithium ion batteries. These prototypes were each small enough to fit into an airline-size carry-on bag. The second prototype, which is approaching the objective requirements, is smaller, uses a new scroll compressor technology, weighs about 10 pounds, and uses a high energy density type of lithium polymer battery. Although the second prototype is a significant improvement over the first, the performance characteristics of the scroll compressor are not well known. For this compressor to be used in a medical device, its failure modes and wear characteristics will have to be well understood; this testing is currently underway. The requirement for oil-free operation significantly increases the compressor complexity. A free piston linear compressor is being evaluated as a back-up design. Development is continuing on both oxygen generators. Thirty pre-production models of the oxygen generator using a reciprocating air compressor are being built for user evaluation.

Special Medical Emergency Evacuation Device



The Special Medical Emergency Evacuation Device (SMEED) is a lightweight platform designed to quickly attach to a North Atlantic Treaty Organization litter. It was designed by SSG Eric Smeed, while stationed at the U.S. Army Institute of Surgical Research for medical evacuation of burn patients. The device is usually mounted over the legs of the patient, although it can be attached anywhere along the length of the litter. The platform has various universal fasteners so that it can be configured in several ways, depending on the mission. It is specifically designed to accommodate all of the Patient Movement Item(s) (PMI) in the Army inventory to include vital signs monitor, infusion pump, aspirator, D-cylinder oxygen tank, ventilator, defibrillator, and has the flexibility to mount other medical devices as required.

More than 300 SMEED systems were deployed with Army, Marine, and Air Force units in support of OEF and OIF. User feedback on this system has been favorable.

The U.S. Army Aviation and Missile Command allowed the SMEED to be flown in theater under an emergency restricted AWR. The USAARL developed and evaluated a new simulation model to aid in obtaining an unrestricted Air Worthiness Release (AWR) for the SMEED. The manufacturer has developed an accessory power supply/battery pack to provide electrical power to the PMIs operated on the SMEED.

Stryker Medical Evacuation Vehicle

The Stryker Medical Evacuation Vehicle (MEV) functions as the medical evacuation variant of the Stryker Armored Vehicle platform for the Stryker Brigade Combat Team (SBCT). Medical capability includes an automated litter lift system, on-board oxygen, suction, storage space for essential medical items and equipment, plus the capacity to carry four litter patients or six ambulatory patients, and a crew of three.

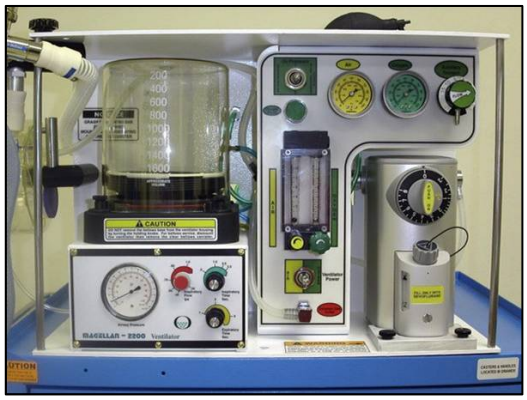
The Stryker MEV was fielded to the first SBCT at Fort Lewis, WA, and is currently deployed for duty in OIF. After-action reports from Iraq indicate that the Stryker is performing well and that deficiencies are being addressed. Reports on the Stryker MEV indicate that the primary issues involve ordering and receiving spare parts for medical unique items, particularly the litter lifting system. The prime contractor, General Dynamics Land Systems, is working to rectify this situation. Discussions to include air conditioning on the fourth and fifth SBCTs are ongoing between PM-SBCT and General Dynamics.

Thawed Blood Processing System

The Thawed Blood Processing System (TBPS) consists of a blood processor and related components that will replace the existing frozen blood system. The current system does not meet military requirements because it is labor-intensive, limits production to a single blood unit per hour per technician, and limits shelf life of processed thawed blood to only one day. The new system is an automated, closed-loop sterile blood-processing system capable of increasing production and shelf life (of processed blood) from the current one day to 14 days. The TBPS also includes a bar code reader for automated data collection, a printer, a newly designed dry thawing device to reduce thaw time from the current 50 minutes in a conventional water bath to less than 10 minutes, and a new blood bag to eliminate the current 20 percent to 50 percent leakage rate. The TBPS processing device is a compact tabletop design. The manufacturer leveraged technology from an existing predicate device to help accelerate regulatory approval. The Armed Services Blood Program Office continued to show interest in this system due to its low cost, small foot print, and speed.

Ventilatory Assist Device

The Ventilatory Assist Device (VAD) is an FDA-approved anesthesia delivery system consisting of an anesthesia apparatus, ventilator, and patient ventilator circuit. The VAD will be used to anesthetize patients during surgical procedures



with the Field Surgical Teams (FST) and Combat Support Hospitals (CSH). The VAD will eliminate the need for the anesthesia provider to hand bag the patient. Manually ventilating a patient is very labor-intensive and reduces the number of surgical procedures that can be performed. The VAD will be compatible with low-pressure oxygen sources such as oxygen concentrators. The use of the VAD will ensure proper patient ventilation during surgery.

In order to further reduce weight, the manufacturer has initiated plans to integrate a ventilator into the VAD that can be powered by either an electrical or compressed gas source. This will eliminate the current need for a separate air compressor while retaining the versatility of using any standard drive source such as a medical or dental air compressor, bottled air or oxygen, or manual ventilation.

The user and subject matter expert evaluations suggested several improvements that have been incorporated into the design.

The ORD has been approved by the Army Requirements Oversight Review Council, and is pending review by the Joint Requirements Oversight Council.

Industrial Services Branch

Introduction

The USAMMDA's Industrial Services Branch (ISB), is a small team of engineering technicians with a vast array of design and fabrication skills. This integrated team works together to design, develop drawing packages, and rapidly prototype far forward medical equipment in support of the USAMRMC. The ISB is capable of rapidly prototyping medical devices in a wide range of scales and variety of materials. These capabilities are also used to harden COTS components, equipment and products for use in a field environment.

Military Relevance

In light of today's environment, the U.S. Army has put a priority on water quality management. Effective water quality testing in tributaries, reservoirs, wells and other municipality's water sources is an ongoing effort and concern both for our military deployed abroad as well as our civilian population.

Submersible Bio-monitoring System

As a result, USAMMDA's Industrial Services Branch, and the U.S. Army Center for Environmental Health Research (USACEHR) have designed, fabricated, and applied for a patent on a unique submersible bio-monitoring device. This system, in real-time, monitors and evaluates water quality based on the biological response of eight bluegills. The known behavior parameters, in various water conditions, of these fish are used as standards to insure water quality. The analysis of these electrical signals, emitted from the fish, are first amplified and then fed into a computer software program that records, evaluates and sends an alarm when those signals represent a potential chemical/toxicity problem.

This ongoing collaborative effort has netted a significant gain in our desire to miniaturize this system. The second generation bio-monitoring device is considerably smaller than its predecessor. The original bio-monitoring system, also built here at USAMMDA approximately 1-2 years ago, was designed for an above water fixed facility water plant, and is the size of a small filing cabinet. Whereas, the second generation model is designed to be totally mobile and submersible, and is literally the size of a shoe box. The size and fact that this unit is submersible opens up a wide range of possibilities for water quality testing both militarily and commercially.

USAMMDA's ISB, with Army unique capabilities, has reached out and teamed with other USAMRMC organizations in support of our common goal: "…provide quality medical products for the U.S. warfighter."

Pharmaceutical Systems

Introduction

The Pharmaceutical Systems Project Management Division (PSPMD) centrally manages the development and acquisition of pharmaceutical and biological products (drugs, vaccines, toxoids, blood products and fluids). These products are fielded as preventive, protective and therapeutic modalities for use against infectious diseases. Product Managers leverage domestic and foreign medical technology to remedy deficiencies identified by the Combat Developer and monitor military, industrial, and university research projects for potential solutions to identified problems.

Military Relevance

U.S. Military Forces must be prepared to serve anywhere in the world against any threat. This could result not only in conventional injuries sustained during combat operations but exposure to chemical and biological warfare agents, as well as exposure to endemic diseases not commonly found in the United States. The development of products against these threats will help save lives, sustain the fighting Force and enhance return to duty.

Adenovirus Vaccine, Types 4 and 7

Adenovirus vaccine has been used exclusively by the military to prevent Adenovirus- related acute respiratory disease (ARD) in Soldiers living in barrack-type environments during basic training. The vaccine is an orally administered, enteric-coated tablet containing live adenovirus serotypes 4 or 7. Prior to the use of adenovirus vaccines, adenovirus types 4 and 7 accounted for 60 percent of all ARD in military recruits who were hospitalized. Adenoviruses are associated with pharyngitis, conjunctivitis, atypical pneumonia, and rhinitis. A contract to develop and manufacture the type 4 and 7 adenovirus vaccines was awarded in 2001 to Barr Laboratories, Inc. The first phase of the contract required an IND application and successful completion of Phase 1 clinical trials. The second phase requires completion of all clinical trials and full FDA licensure of the product. The vaccines are expected to be available early in 2008. Barr completed building construction of the adenovirus manufacturing facility at their Forest, Virginia, laboratory site. All equipment was installed and qualifications performed.

An IND for the new adenovirus vaccines was submitted to the Food and Drug Administration (FDA) in July of 2004. A Phase 1 clinical trial was successfully completed at Fort Sam Houston, Texas in the fall of 2004 under the supervision of investigators from Barr and the Walter Reed Army Institute of Research. Results from this trial are currently being analyzed. Clinical trials required for licensing of the vaccines are now in planning and are scheduled for initiation late-summer to fall of 2005.

Dengue Tetravalent Vaccine (DTV)

The dengue tetravalent vaccine (DTV) is a live-attenuated virus vaccine for prevention of dengue fever. The DTV contains all four monovalent serotypes grown in fetal Rhesus lung (FRhL) cell culture. The DTV is being developed in collaboration with GlaxoSmithKline Biologicals (GSK). In CY03, Phase 1 trials were conducted to test the safety and immunogenicity of two different tetravalent vaccine formulations (formulations 17 and 18), and to assess the safety and immunogenicity of an intradermal route of administration.

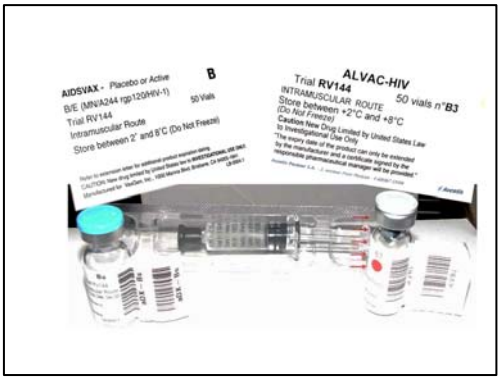
Phase 1 and early phase 2 studies of the DTV were continued in CY04 to further assess the safety and immunogenicity of DTV in different populations. Studies were initiated in Thailand through the Armed Forces Research Institute of Medical Sciences (AFRIMS) supported by the WRAIR. An additional study was initiated by GSK in Panama.

Hepatitis E Virus Vaccine (HEVV)

The HEVV consists of a purified polypeptide produced in insect cells infected with a recombinant baculovirus containing truncated hepatitis E virus (HEV) genomic sequences encoding the viral capsid antigen. The recombinant HEV protein is formulated with an aluminum salt adjuvant. The HEVV is designed to protect DoD personnel and their families from hepatic disease caused by infection with the HEV. This vaccine is also being developed in collaboration with GSK Biologicals.

A Phase 2, prospective, randomized, double-blind, placebo-controlled (vaccine placebo 1:1) field efficacy trial of the HEVV was started in Royal Nepal Army personnel in Kathmandu in 2001. The 2,000 volunteers received placebo or 20 micrograms of HEV recombinant protein at 0, 1 and 6 months. The study was conducted through AFRIMS with support from the WRAIR. The study was completed in 2004 and data is currently being compiled in a report which will be released in the spring of 2005. Future plans for further development and licensure are under negotiation between the USAMRMC and GSK.

Human Immunodeficiency Virus (HIV) Vaccine



The U.S. military has focused its HIV vaccine efforts on the development of vaccines which would be protective against viral strains found outside the United States where Forces may be deployed. The HIV vaccine currently in advanced development focuses on the strains prevalent in Southeast Asia. The strategy combines two vaccines: a priming inoculation that is designed to stimulate the cellular immune system, and a boosting inoculation that is designed to stimulate the humoral immune system. The former is ALVAC-HIV (vCP1521), an attenuated canarypox virus which carries HIV genes; the latter vaccine is AIDSVAX® B/E gp120, bivalent synthetic glycoproteins from the surfaces of the two types of HIV found in Thailand. The Phase 3 trial which is underway to determine the efficacy of this vaccine strategy is led by a Principal Investigator and several hundred staff from the Ministry of Public Health of Thailand, along with Mahidol University and the Royal Thai Army. Sharing sponsorship of this trial with the Army is the NIH; other collaborators include the WRAIR, AFRIMS, Aventis Pasteur, VaxGen, The Henry M. Jackson Foundation, The EMMES Corporation and Quintiles.

The clinical trial is designed to determine the ability of the vaccine combination to protect against HIV infection or to modify the rate of disease progression. The trial will enroll 16,000 adult subjects, with half receiving vaccine and half receiving placebo in a double-blinded manner. Following enrollment and immunization, subjects are followed for another three years to detect the occurrence of HIV infections. As of the end of 2004, more than 8,600 volunteers had enrolled in the trial and begun vaccination. Oversight is provided by a Data and Safety Monitoring Board and a Pharmacovigilance Committee, both with international membership. The study will be completed in 2009.

Leishmania Skin Test

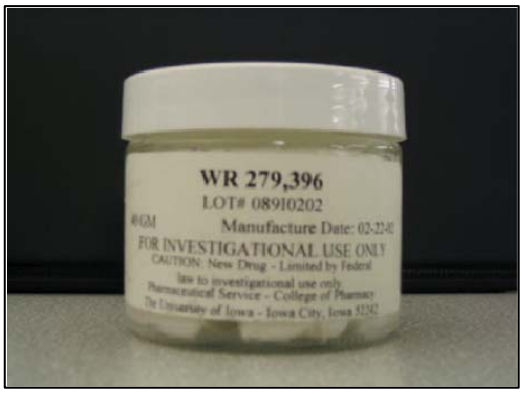
The disease leishmaniasis occurs in 88 countries around the world and is caused by protozoan parasites transmitted to humans from the bite of an infected sand fly than a million new cases of human leishmaniasis are reported annually in the world. Currently, some 12 million people throughout the world suffer from leishmaniasis.

The Leishmania Skin Test (LST) is designed to be used to screen U.S. Servicemembers who may have been exposed to Leishmania species (parasites) after deployment to Leishmania-endemic areas. The skin test for Leishmania is

made according to the same general principles as the skin test for tuberculosis. The Leishmania test is performed by injecting a small amount of purified Leishmania proteins under the skin and then measuring any local skin reaction 48-72 hours later. A small bump of 5mm or greater is a positive indication that the individual has been exposed to the Leishmania parasite.

As a result of a reevaluation of program priorities, in light of funding available for development efforts, a contract currently in place with Allermed Laboratories, Inc., to produce the LST was placed in a termination phase. Allermed will continue to work on the LST without additional Government funding until the end of CY05 at which time the current contract will be terminated unless an alternate source of funding is identified by Allermed.

Topical Antileishmanial Drug, Paromomycin/Gentamicin



Nearly every American Soldier serving in the Middle East in support of OEF and OIF is at risk of exposure to Leishmaniasis. Accordingly, cutaneous leishmaniasis (CL) has been a relatively common infection among deployed Soldiers and, as of this date, more than 850 patients have been positively diagnosed and treated. The current standard of care for the treatment of CL is sodium stibogluconate (Pentostam) which is only available at the Walter Reed Army Medical Center (WRAMC) and at the Brooke Army Medical Center (BAMC) as an investigational drug under IND. As an investigational drug, treatment with Pentostam requires evacuation of the infected Soldier to one of these medical centers for 10-20 days of daily IV infusions and has resulted in a cost of over ~$10M since the start of OIF/OEF. Furthermore, Pentostam is associated with significant side effects and toxicities, which include vomiting, diarrhea, pancreatitis, elevated liver enzymes and at higher doses, pulmonary edema. For many patients, the risks associated with Pentostam outweigh the benefits: although CL is a disfiguring disease, it is also usually non-life threatening.

Over the past few years, researchers in MRMC have developed a highly effective topical agent to treat CL based on a combination of two aminoglycoside antibiotics, paromomycin sulfate (15%) and gentamicin sulfate (0.5%), that are formulated in a cream base. This drug is superior in many ways to Pentostam and, once approved, it can be used by infected Soldiers within the theater of operations thus obviating the need to evacuate troops from their units. A preliminary analysis of data from a recent Phase 2 clinical trial suggests a cure rate of 95% by day 80 with a twice-daily administration for the first 20 days. These results support a previous Phase 2 study in which the drug demonstrated

a 71% cure rate when used twice a day for 20 days in Columbian cutaneous leishmaniasis. We are currently scaling GMP production of the formulated drug product to conduct a Phase 3 trial in order to support filing an NDA with the U.S. FDA.

Malaria Rapid Diagnostic Device (MRDD)

The Malaria Rapid Diagnostic Device (MRDD) will be an FDA-approved field deployable, handheld, disposable point-of-care test to rapidly detect the presence of malaria parasites found in the blood samples of patients displaying symptoms of malaria. The MRDD will not require the use of additional equipment to analyze appropriate clinical specimens. The MRDD will facilitate the early diagnosis of malaria infection and prompt medical intervention. Malaria, in its various forms, constitutes a serious infectious disease threat to the U.S. Forces, including operations other than war, in all tropical and subtropical regions of the world. The 80,000 malaria cases in Vietnam resulted in a loss of more than a million man-hours. Similarly, in Operation Restore Hope (Somalia) and Operation Uphold Democracy (Haiti), numerous Soldiers contracted malaria. Malaria is an acute infection with high morbidity (severe illness) and the potential to rapidly incapacitate large numbers of personnel. Because one type of malaria is often fatal if untreated in non-immune individuals, the diagnosis of malaria must be accomplished for any Servicemember with fever occurring during or after sojourns in a malaria-endemic region. Even though there are MRDDs marketed outside of the United States, U.S. Forces cannot use them until the MRDDs are approved by the FDA for commercial sale in the United States. To that end, for the MRDD, a 510(k) Premarket Notification must be submitted to the FDA. A 510(k) is a scientific regulatory document by which the FDA evaluates the safety and effectiveness of medical devices.

In CY04, a trial comparing the diagnostic accuracy and performance of the BINAX NOW® ICT Malaria Test on specimens collected by venous and fingerstick sampling was completed at AFRIMS with support from the WRAIR and the data is currently being analyzed. In CY03 the FDA determined that the MRDD can be submitted as a de novo 510(k) Premarket Notification versus the previous requirement that the submission be a Premarket Approval Application (PMA). This change is likely to shorten the FDA's internal review time of the submission from one year to three months. A final clinical study, called a True-Negative Clinical Protocol, will be conducted in CY05 and the 510(k) will be submitted by Binax.

Malaria Recombinant Vaccine With Adjuvant Combinations (RTS,S)

The RTS,S malaria vaccine, which is being developed in collaboration with GlaxoSmithKline Biologicals, to protect U.S. Forces from falciparum malaria. The RTS,S vaccine consists of recombinantly engineered immunogenic fractions of the malaria sporozoite surface coat co-expressed with protective epitopes from the hepatitis B surface antigen. During purification, these proteins self-assemble into particles that form the antigenic component of the vaccine. The vaccine, delivered by intramuscular injection, is formulated in a liquid emulsion containing potent immunostimulants (designated as AS02A) that dramatically enhance the immune response to the RTS,S particles. The lead laboratory is WRAIR. In an effort to enhance the immunogenicity and duration of protection, the RTS,S vaccine is being tested in combination with a new, proprietary adjuvant system (AS01B) and evaluated in a Phase 1/2a safety, immunogenicity and preliminary efficacy trial in U.S. volunteers. The study was initiated at the WRAIR Clinical Trials Center in CY04. Results of the trial will be evaluated in mid-CY05 to determine the future direction for this vaccine.

Diarrheal Diseases Vaccines

During CY04, three vaccines under development for prevention of diarrheal diseases in deployed U.S. Forces were de-transitioned back into the technology base for re-evaluation. Development efforts were discontinued for the Shigella flexneri Vaccine (SC602), the ETEC Whole Cell, Recombinant B Subunit Vaccine, and the Campylobacter Whole Cell (CWC) Vaccine.

Combined Camouflage Face Paint (CCFP)

Camouflage face paint now offers more than simple concealment. The new Combined Camouflage Face Paint (CCFP) in stick-type dispensers will be a U.S. Environmental Protection Agency (EPA) registered blend of face paint with DEET insect repellent to provide a minimum of 8 hours of protection against biting insects. Inclusion of insect repellent protection will reduce nuisance factors by repelling insects near the face and help reduce diseases (e.g., malaria and dengue fever) transmitted by biting insects. All CCFP formulations will be used by individual Soldiers for protection against biting insects, protection against detection by night vision goggles (the face paint reduces a Soldier's near-infrared signature), and for blending into the environment in all military missions.

During CY03, technical issues with performance of temperature storage chambers were identified. Contracted maintenance began to address the re-validation of all three chambers. Preliminary stick formulations underwent technical testing by our Industry Partner. The Natick Soldier Center provided a Soldier Market Survey that addressed their “likes” and “dislikes” of the currently fielded two-color camouflage face paint sticks. In CY04, visual color evaluations of the new stick formulations were performed by Natick Soldier Center. Additionally, plans were prepared for required non-clinical safety testing of the stick formulations to meet regulations of the EPA. In CY05 the non-clinical testing will be completed and the initial clinical efficacy trial will be conducted at the WRAIR under laboratory controlled conditions. The lead laboratory for efficacy is WRAIR. The lead laboratory for camouflage is The Natick Soldier Center.

Hemoglobin-Based Oxygen Carrier (HBOC)

Hemoglobin-based oxygen carriers (HBOC) consist of purified, cell-free hemoglobin (either human or bovine) in physiologic solutions that are intended to provide fluid replacement combined with capacity to carry and deliver oxygen to vital tissues in patients who have suffered serious hemorrhage and require red blood cells but red blood cells are not available. Several candidate products are in various stages of development by small, private manufacturers. At least two products (PolyHeme®, Northfield Laboratories, Inc, Evanston, IL and Hemopure®, Biopure Corp., Cambridge, MA) are in, or are ready to begin, Phase 3 pivotal testing for licensure.

In 2004, USAMMDA worked with USSOCOM to develop an IND treatment protocol in collaboration with Northfield Laboratories, Inc., using PolyHeme® which began pivotal Phase 3 testing for licensure in December 2003. The principal obstacle to fielding of this product is relatively poor tolerance of ambient temperatures and limited usability (approximately 30 to 60 hours) after removal from refrigeration. During 2004, the HBOC Work Group conducted temperature monitoring and recording of ambient temperatures in Iraq during the summer and fall months to help determine parameters for further temperature stability studies. Fielding of the IND treatment protocol is anticipated no earlier than January 2006.

Antimalarial Drug, Tafenoquine (WR238605)

Tafenoquine (WR238605) is an 8-aminoquinoline that has demonstrated antimalarial potential in both pre-clinical and clinical studies. While it has demonstrated potential both as a prophylactic and treatment drug, the original acquisition strategy was focused on development of tafenoquine for prophylaxis of Plasmodium falciparum malaria.

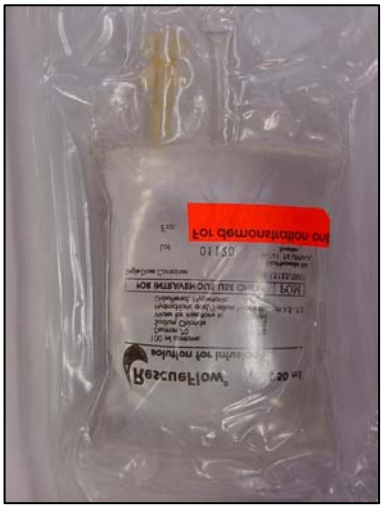
Based on the results of an initial field study carried out from late 2000 to early 2001 in Australian Soldiers deployed to East Timor comparing tafenoquine to mefloquine, the FDA placed a hold on the tafenoquine IND pending further safety studies. Additional safety data were presented to the FDA in December 2002, after which the FDA allowed the tafenoquine IND to be re-activated effective January 19, 2003. Per FDA direction, a Phase 1 safety trial was subsequently initiated in July 2003 at the Uniformed Services University of the Health Sciences in Bethesda, MD, to closely examine normal volunteer subjects in a double-blind, placebo-controlled prospective fashion for any evidence of effects on renal function or visual function due to administration of tafenoquine. A second study site for this trial was opened in the United Kingdom in late summer 2004.

In parallel with these safety issues, the USAMRMC industry partner for development of tafenoquine, GlaxoSmithKline, determined that they could not ethically support Phase 3 prospective clinical trials to investigate the efficacy and safety of tafenoquine for the prophylaxis of malaria in populations where the drug would not be commercially available. This made proving efficacy of tafenoquine for prophylaxis extremely difficult and caused a re-evaluation of the acquisition strategy. A group of DoD malaria experts led by personnel from the WRAIR was convened to address the issue. The result was a recommendation that the strategy be shifted to focus on development of tafenoquine as a radical cure for treatment of Plasmodium vivax malaria which has been rapidly emerging as the DoD's primary malaria threat. Negotiations are currently underway with GSK to further define this strategy.

Tick-Borne Encephalitis Virus Vaccine

Tick-borne Encephalitis (TBE) is a viral infection of the central nervous system transmitted to people by infected ticks. This disease is endemic in several European countries, Russia, and China. Transmission is seasonal and occurs between April and November, particularly in forest and rural areas. The incubation period averages 7-14 days, followed by 1-8 days of fever and flu-like symptoms. Encephalitis occurs in up to 30 percent of infected individuals, requiring many weeks of hospitalization and rehabilitation. Mortality is 1-2 percent in general, but can be as high as 23 percent in the Far East. Once infected, there is no effective curative treatment, only supportive care. However, a TBE virus vaccine has been used in Europe for over 20 years to prevent illness due to TBE virus infection. The vaccine is licensed for use in Europe, but it is not licensed in the U.S.

During CY04, the TBE vaccine effort remained unfunded due to limited availability of development funds and the relatively low priority of TBE against other infectious disease threats. A potential industrial partner submitted a National Institute of Allergy and Infectious Diseases (NIAID) Challenge Grant application for funding support to reach U.S. licensure, but the grant was turned down. Efforts are continuing to find an alternative source of funding.

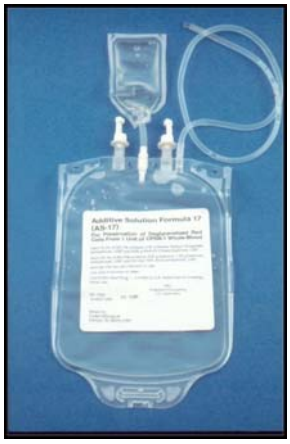


Hypertonic Saline Dextran (HSD)

Hypertonic Saline Dextran (HSD) is a resuscitation fluid that utilizes 6% high molecular weight dextran and 7.5% sodium chloride. The potential advantage of HSD compared to usual physiologic resuscitation fluids (e.g., 0.9% sodium chloride and Ringer's lactate) is manifold, including reduced logistical load for field medics, improved hemodynamic response in resuscitated patients, and modulation of harmful immune responses after severe shock and resuscitation. The HSD is manufactured by a Swedish company (Biophausia AB) and is approved for use in Europe but not in the United States.

In 2004, the Army began collaboration with the National Heart, Lung, and Blood Institute (NHLBI) to compare HSD to traditional resuscitation fluids for treatment of trauma patients in the United States. The NHLBI has planned a study anticipated to begin in late 2005 that, if successful, will result in FDA approval for marketing in the United States for treatment of trauma. FDA approval is not anticipated before 2008.

Red Blood Cells, Extended Life (RBCXL)



Red Blood Cells, Extended Life (RBCXL) is a new additive solution and blood collection system that extends the life of stored, packed red blood cells from 6 weeks to at least 8 weeks. The key to the new process is a new additive solution and a new bag system for collection and storage. Both the additive solution and the bag system have been developed by the University of Cincinnati and the Army over the past 15 years.

During 2004, the Army and the University of Cincinnati worked to settle intellectual property issues and to identify a corporate partner to complete development and bring the new process to market. In 2004, a manufacturer, Hemerus Medical, St. Paul, MN, was licensed exclusively to complete development and marketing. In 2005 to 2007, development will be continued by Hemerus and the Army, including

completion of pre-clinical and clinical development and finalization of collection system design and production issues.

Platelet-Derived Hemostatic Agent (PDHA)

Platelet-derived hemostatic agent (PDHA) is an agent intended to enhance blood clotting in combat casualties who have had severe hemorrhage and have developed coagulopathy and continue to bleed despite definitive surgical efforts to stop bleeding. Use of fresh platelets is not a readily available option in forward hospitals on the battlefield because of a very short shelf-life (5 days). Use of fresh whole blood (FWB) to replace platelets is an option but has potential risks as well. There are multiple candidate products derived from human platelets, including frozen platelets developed by the US Navy and freeze-dried platelet products developed by DARPA (FDP-Tä, Adlyfe, Inc., Rockville, MD) and by the U.S. Navy (Stasixä, Hemocellular Therapeutics, Inc, Chapel Hill, NC). Platelets frozen in DMSO, developed by the Naval Blood Research Laboratory (NBRL) in Boston, MA, appear to be closest to completion of development.

In 2004, the Army began negotiations with the U.S. Navy Bureau of Medicine and NBRL to transfer sponsorship of the frozen platelet process to the Army for continued development. The Army is developing plans for completion of development with a target of 2010 for FDA approval.